Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in this application. The following amendments do not constitute an admission regarding the patentability of the amended subject matter and should not be so construed. Applicant reserves the right to pursue the subject matter of the canceled claims in this or any other appropriate patent application.

Claims 4, 13, and 47-59 have been amended to remove multiple dependencies. Please cancel claims 19-38 without prejudice to or disclaimer of the subject matter contained therein. Claims 1-18 and 39-59 are now pending.

Complete Listing of Claims:

1. (Original) A method of determining the tissue selectivity of a ligand for a co-regulator dependent target molecule comprising:

(a) providing a set of ligands that modify the stability of the target molecule; and

(b) screening one or more ligands of said set for their ability to further modify the stability of the target molecule in the presence of one or more tissue-selective co- regulators for the target molecule; wherein a further modification of stability of the target molecule in the presence of a ligand of said set and a co-regulator of said one or more tissue-selective co-regulators indicates whether the ligand is an agonist or an antagonist of the target molecule when in the presence of said tissue-selective co-regulator, thereby determining the tissue selectivity of the ligand for the target molecule.

2. (Original) The method of claim 1, wherein providing the set of ligands that modify the stability of the target molecule comprises screening one or more of a multiplicity of different ligands for their ability to modify the stability of the target molecule.

3. (Original) The method of claim 2, wherein said screening of one or more of a multiplicity of different ligands comprises:

(a) contacting said target molecule with one or more ligands in each of a multiplicity of containers;

(b) treating said target molecules in each of said multiplicity of containers to cause said target molecule to unfold;

(c) measuring in each of said containers a physical change associated with the unfolding of said target molecules;

(d) generating an unfolding curve for said target molecule for each of said containers;

(e) comparing each of said unfolding curves in step (d) to:

(i) each of the other unfolding curves; and/or
(ii) the unfolding curve for said target molecule in the absence of any of said multiplicity of different ligands ; and(f) determining whether any of said ligands modifies the stability of said target molecule, wherein a modification in stability is indicated by a change in said unfolding curve.

4. (Presently Amended) The method of claim 1 ~~or claim 3~~, wherein said screening step further comprises:

(a) contacting said target molecule and one or more molecules of said set with one or more of said co-regulators in each of a multiplicity of containers;

(b) treating said target molecules in each of said multiplicity of containers to cause said target molecule to unfold;

(c) measuring in each of said containers a physical change associated with the unfolding of said target molecules;

(d) generating an unfolding curve for said target molecule for each of said containers;

(e) comparing each of said unfolding curves in step (d) to:

(i) each of the other unfolding curves; and/or

(ii) the unfolding curve for said target molecule in the absence of (1) any of said ligands of said set and/or (2) said co-regulators; and

(f) determining whether any of said ligands of said set further modifies the stability of said target molecule, wherein a further modification in stability is indicated by a further change in said unfolding curve.

5. (Original) The method of claim 1, wherein said one or more co-regulators includes a co-activator and/or a co-repressor.

6. (Original) The method of claim 5, wherein one or more ligands of the set further modify the stability of the target molecule in the presence of a co-activator, thereby identifying the ligand as an agonist of the target molecule when in the presence of the co-activator.

7. (Original) The method of claim 6, wherein the agonist is a partial agonist.

8. (Original) The method of claim 5, wherein one or more molecules of the set further modify the stability of the target molecule in the presence of a co-repressor, thereby identifying the ligand as an antagonist of the target molecule when in the presence of the co-repressor.

9. (Original) The method of claim 8, wherein the antagonist is a partial agonist.

10. (Original) A method of determining the tissue selectivity of a ligand for a co-regulator dependent target molecule comprising:

(a) providing a set of ligands that shift the thermal unfolding curve of the target molecule; and

(b) screening one or more ligands of the set for their ability to further shift the thermal unfolding curve of the target molecule in the presence of one or more tissue- selective co-regulators for the target molecule; wherein a further shift in the thermal unfolding curve of the target molecule in the presence of a ligand of the set and a co-regulator of said one or more tissue-selective co-

regulators indicates whether the ligand is an agonist or an antagonist of the target molecule when in the presence of said tissue-selective co-regulator, thereby determining the tissue selectivity of the ligand for the target molecule.

11. (Original) The method of claim 10, wherein providing the set of ligands that shift the thermal unfolding curve of the target molecule comprises screening one or more of a multiplicity of different ligands for their ability to shift the unfolding curve of the target molecule.

12. (Original) The method of claim 11, wherein said screening of one or more of a multiplicity of different ligands further comprises:

(a) contacting said target molecule with one or more of said multiplicity of different ligands in each of a multiplicity of containers ;

(b) heating said target molecules in each of said multiplicity of containers to cause said target molecule to unfold;

(c) measuring in each of said containers a physical change associated with the thermal unfolding of said target molecules resulting from said heating;

(d) generating a thermal unfolding curve for said target molecule as a function of temperature for each of said containers;

(e) comparing each of said unfolding curves in step (d) to:

(i) each of the other thermal unfolding curves; and/or

(ii) the thermal unfolding curve for said target molecule in the absence of any of said multiplicity of different ligands; and

(f) determining whether any of said multiplicity of different ligands shift the thermal unfolding curve of said target molecule.

13. (Presently Amended) The method of claim 10 ~~or claim 12~~, wherein said screening step further comprises:

(a) contacting said target molecule and one or more ligands of said set with one or more of said co-regulators in each of a multiplicity of containers;

(b) heating said target molecules in each of said multiplicity of containers to cause said target molecule to unfold;

(c) measuring in each of said containers a physical change associated with the thermal unfolding of said target molecules resulting from said heating;

(d) generating a thermal unfolding curve for said target molecule as a function of temperature for each of said containers;

(e) comparing each of said thermal unfolding curves in step (d) to:

(i) each of the other thermal unfolding curves; and/or

(ii) the thermal unfolding curve for said target molecule in the absence of(1) any of said ligands of said set and/or (2) said co-regulators; and

(f) determining whether any of said molecules of said set further shifts the thermal unfolding curve of said target molecule.

14. (Original) The method of claim 10, wherein said one or more co-regulators includes a co- activator and/or a co-repressor.

15. (Original) The method of claim 10, wherein one or more ligands of the set further modify the stability of the target molecule in the presence of a co-activator, thereby identifying the ligand as an agonist of the target molecule when in the presence of the co-activator.

16. (Original) The method of claim 15, wherein the agonist is a partial agonist.

17. (Original) The method of claim 10, wherein one or more ligands of the set further modify the stability of the target molecule in the presence of a co-repressor, thereby identifying the ligand as an antagonist of the target molecule when in the presence of the co- repressor.

18. (Original) The method of claim 17, wherein the antagonist is a partial agonist.

19. (Cancelled)

20. (Cancelled)

21. (Cancelled)

22. (Cancelled)

23. (Cancelled)

24. (Cancelled)

25. (Cancelled)

26. (Cancelled)

27. (Cancelled)

28. (Cancelled)

29. (Cancelled)

30. (Cancelled)

31. (Cancelled)

32. (Cancelled)

33. (Cancelled)

34. (Cancelled)

35. (Cancelled)

36. (Cancelled)

37. (Cancelled)

38. (Cancelled)

39. (Original) A method of determining the tissue selectivity of a ligand for a co-regulator dependent target molecule having an unknown function comprising:

(a) providing a set of ligands that modify the thermal unfolding curve of a target molecule having an unknown function, wherein said set of ligands modify the thermal unfolding curve of receptors which share biological function; and

(b) screening one or more ligands of said set for their ability to further modify the thermal unfolding curve of the target molecule in the presence of one or more co- regulators; wherein a further modification of the thermal unfolding curve of the target molecule in the presence of a ligand of said set and a co-regulator of said one or more co-regulators indicates whether the molecule is an agonist or an antagonist of the target molecule when in the presence of said co-regulator.

40. (Original) The method of claim 39, wherein providing the set of ligands that modify the thermal unfolding curve of the target molecule comprises screening one or more panels of ligands which modify the thermal unfolding curve of receptors which share biological function for their ability to modify the thermal unfolding curve of the target molecule.

41. (Original) The method of claim 39, wherein the ligand is a partial agonist of the target molecule when in the presence of a co-activator.

42. (Original) The method of claim 39, wherein the ligand is a partial agonist of the target molecule when in the presence of a co-repressor.

43. (Original) A method of determining the tissue selectivity of a ligand for a co-regulator dependent target molecule having an unknown function comprising:

(a) providing a set of ligands that modify the stability of a target molecule having an unknown function, wherein said set of ligands modify the stability of receptors which share biological function ; and

(b) screening one or more ligands of said set for their ability to further modify the stability of the target molecule in the presence of one or more co-regulators; wherein a further modification of the stability of the target molecule in the presence of a ligand of said set and a co-regulator of said one or more co-regulators indicates whether the molecule is an agonist or an antagonist of the target molecule when in the presence of said co-regulator.

44. (Original) The method of claim 43, wherein providing the set of molecules that modify the stability of the target molecule comprises screening one or more panels of ligands which modify the stability of receptors which share biological function for their ability to modify the stability of the target molecule.

45. (Original) The method of claim 43, wherein the ligand is a partial agonist of the target molecule when in the presence of a co-activator.

46. (Original) The method of claim 43, wherein the ligand is a partial agonist of the target molecule when in the presence of a co-repressor.

47. (Presently Amended) The method of claim[[s]] 1[[- 46]], wherein the target molecule is selected from androgen receptor, glucocorticoid receptor, estrogen receptor, progesterone receptor, GPCR,NF-KB, steroid receptor co-activator (src), and Jac.

48. (Presently Amended) The method of claim[[s]] 1[[- 46]], wherein the target molecule is a nuclear receptor.

49. (Presently Amended) The method of claim[[s]] 1[[- 46]], wherein the target molecule is a G-protein coupled receptor.

50. (Presently Amended) The method of claim[[s]] 1[[- 46]], wherein the target molecule is an estrogen receptor.

51. (Presently Amended) The method of claim[[s]] 1[[- 46]], wherein the target molecule is ER-a.

52. (Presently Amended) The method of claim[[s]] 1[[- 46]], wherein the target molecule is ER-.

53. (Presently Amended) The method of claim[[s]] 1[[- 46]], wherein the target molecule is PPAR-Y.

54. (Presently Amended) The method of claim[[s]] 1[[- 46]], wherein the target molecule is a tyrosine kinase.

55. (Presently Amended) The method of claim[[s]] 1[[- 46]], wherein the target molecule is NF-xB.

56. (Presently Amended) The method of claim[[s]] 1[[- 46]], wherein one or more of the co-regulators are selected from SRC-1, SRC-2, and SRC-3.

57. (Presently Amended) The method of claim[[s]] 1[[- 46]], where in the co-regulator is selected from Gsa,Gia, Gta, Gqa, Goa,Gqa, IlcB, SH2 and SOCS.

58. (Presently Amended) The method of claim[[s]] 1[[- 46]], wherein the ligand is a steroid.

59. (Presently Amended) The method of claim[[s]] 1[[- 46]], wherein the ligand is a non-steroidal ligand.